Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-45 and 48-65 are pending in the application, with claim 1 being the sole independent claim. Claims 69-80 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claims 37, 45 and 48-52* are withdrawn from consideration by the Examiner as being drawn to non-elected inventions or non-elected species, but remain pending.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Claim Rejections Under 35 U.S.C. § 103

A. Marasco In View of Waterhouse

Claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71 and 75-79 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Marasco *et al.*, U.S. Patent No. 5,851,829 ("Marasco") in view of Waterhouse *et al.*, *Nucl. Acids Res. 21*:2265-2266 (1993) ("Waterhouse"), as evidenced by International Committee on Taxonomy of Viruses and Wikipedia, the Free Encyclopedia. (Office Action, page 3). Applicants respectfully traverse this rejection.

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* On the Office Action Summary page, claim 58 is listed as being withdrawn from consideration, but on page 2 of the Office Action, the Examiner stated that claim 58 is no longer withdrawn from consideration. Applicants assume that the designation of claim 58 as being withdrawn from consideration on the Office Action Summary page was an error. Clarification is respectfully requested.

A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). A showing of combinability of references, in whatever form, must be "clear and particular." *See In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617.

As explained below, not all of the elements of the claims are taught or suggested by the currently pending claims. In addition, a person of ordinary skill in the art would not have been motivated to combine or modify the teachings of the cited references. Therefore, a *prima facie* case of obviousness has not been established.

1. Not All Elements of the Claims Are Taught or Suggested by the Cited References

Independent claim 1 is directed, in general terms, to a screening method that identifies polynucleotides that encode an intracellular immunoglobulin molecule or a fragment thereof. Expression of the immunoglobulin induces a modified phenotype in a eukaryotic host cell by binding to an intracellular antigen.

The method of claim 1 comprises, *inter alia*, introducing a first and a second library of polynucleotides into a eukaryotic host cell. The polynucleotides of the first library encode a plurality of first intracellular immunoglobulin subunit polypeptides, each comprising a first immunglobulin variable region. The first immunglobulin variable region is selected from the group consisting of a heavy chain variable region and a light chain variable region. Similarly, the polynucleotides of the second library encode a plurality of second intracellular immunoglobulin subunit polypeptides, each comprising a second immunoglobulin variable region. Like the first immunoglobulin variable region, the second immunoglobulin variable region is selected from the group consisting of a heavy chain variable region and a light chain variable region. Claim 1 specifies that the second immunoglobulin variable region is not the same as the first immunoglobulin variable region. Claim 1 also specifies that the second intracellular immunoglobulin subunit polypeptides combine with the first intracellular immunoglobulin polypeptides to form a plurality of intracellular immunoglobulin molecules, or fragments thereof. The expression of the plurality of intracellular immunoglobulin molecules, or fragments thereof, is permitted in the population of host cells under conditions wherein the modified phenotype can be detected. Finally, the method of claim 1 comprises recovering polynucleotides of the first library from the individual host cells that exhibit the modified phenotype.

The method of claim 1 therefore involves, *inter alia*, the intracellular combination of (1) an immunoglobulin subunit polypeptide comprising a heavy chain (or light chain) variable region, and (2) an immunoglobulin subunit polypeptide comprising a light chain (or heavy chain) variable region, to form (3) an intracellular immunoglobulin molecule (or

fragment thereof). If the intracellular immunoglobulin molecule is able to bind to an intracellular antigen and thereby induce a modified phenotype, the cells are identified and the polynucleotides from the first library are recovered. By this method, one can identify from a library of polynucleotide molecules those that encode an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region that is capable of binding to a specific antigen. This process represents a unique screening method that is neither taught nor suggested by the cited references.

(a) The Cited References Do Not Teach or Suggest a Screening Method of the Present Claims

The cited references do not teach or suggest a method of selecting polynucleotides which encode an intracellular immunoglobulin molecule or fragment thereof, whose expression induces a modified phenotype in a eukaryotic host cell upon binding to an intracellular antigen. The Examiner, however, stated that:

> Marasco et al. (see entire document) disclose a method of selecting polynucleotides which encode an intracellular immunoglobulin molecule, or fragment thereof, including a single-chain immunoglobulin whose expression induces a modified phenotype in a eukaryotic host cell.

(Office Action, pages 3-4). Applicants respectfully disagree. Marasco is not concerned with methods for selecting polynucleotides; rather, Marasco refers broadly to *therapeutic methods* that involve the intracellular binding of an antibody to a target molecule so as to disrupt the normal activity of the target molecule. As explained by Marasco:

> We have now discovered a method by which one can *target an undesired molecule* (sometimes referred to as a target molecule or target antigen), preferably a protein. This method comprises the

> intracellular expression of an antibody capable of binding to the target. A DNA sequence containing a sufficient number of nucleotides coding for the portion of an antibody capable of binding to the target operably linked to a promoter that will permit expression of the antibody in the cell(s) of interest (antibody cassette) is delivered to a cell. Thereafter, the antibody is expressed intracellularly and binds to the target, *thereby disrupting the target from its normal actions*.

(Marasco, column 2, lines 30-41, emphases added). It is clear from this passage that the purpose of the invention set forth in Marasco is to interfere with the normal activities of undesired intracellular target molecules.

The Examiner has cited to Marasco at columns 31 and 32 which, according to the Examiner, disclose "the synthesis and screening of mutant libraries of intracellular immunoglobulin fragments." (Office Action, page 4). The portion of Marasco cited by the Examiner refers to the construction and expression of mutant single chain antibodies (sFv) that specifically bind to the HIV envelope glycoprotein gp120. (*See* Marasco, column 30, line 46, through column 31, line 52). The sFv of Marasco, referred to as "F105," is single molecule consisting of an antibody light chain linked to an antibody heavy chain via a linker. (*See* Marasco, Fig. 2). Marasco used PCR-based mutagenesis to create nucleic acid molecules that encoded variants of F105 containing mutations in the CDR3 of the heavy chain variable domain. (Marasco, column 31, lines 10-47). As noted by Marasco, "mutants having different binding affinities to the envelope glycoprotein were screened." (Marasco, column 31, lines 41-42).

Thus, the purpose of the screening process mentioned in Marasco was *not* to select for polynucleotides which encode a first intracellular immunoglobulin subunit polypeptide

that, when combined with a second intracellular immunoglobulin subunit polypeptide, form an intracellular immunoglobulin molecule that binds to an intracellular antigen and thereby induces a modified cellular phenotype. Instead, the screening of Marasco was conducted simply to identify sFv mutants with "different binding affinities to the envelope glycoprotein." Binding of the sFv mutants to the HIV glycoprotein would not induce a "predetermined modified phenotype" in the cells. The screening mentioned in Marasco at columns 30-32 is therefore far outside the scope of the screening methods encompassed by the present claims.

(b) The Cited References Do Not Teach or Suggest Recovering Polynucleotides from Host Cells Which Exhibit a Modified Phenotype

Claim 1 of the present application recites: "(e) recovering polynucleotides of said first library from those individual host cells which exhibit said modified phenotype." The cited references do not teach or suggest recovering polynucleotides from host cells. The Examiner, however, asserted that:

> Marasco also disclose (e) recovering polynucleotides of said first library from those individual host cells which exhibit said modified phenotype (e.g., see column 31, lines 44-50, "Using the above-described technique, six mutant sFv105 antibodies were produced in which the amino acids in the CDR3 region of the heavy chain were replaced by random amino acids. One of the six mutants [recovered] designated R had a CDR3 region which coded for (SEQ ID NO:74)").

(Office Action, page 6). The cited section of Marasco does not disclose or suggest recovering polynucleotides from host cells that exhibit a modified phenotype. The word "recovered" in brackets at page 6 of the Office Action was inserted by the Examiner and is

not found in the portion of Marasco cited by the Examiner. In fact, Marasco does not mention recovering polynucleotides from cells at all. The "above-described technique" referred to in Marasco is as follows:

> The unique CDR3 mutants were established by PVU2 digestion. Then the entire antibody cassette was removed by HindIII-Xba I digestion, which removes the entire antibody cassette along with cloning sites. These mutant antibodies were then gel-purified, gene cleaned and cloned into pRC/CMV that had been digested with HindIII and XbaI. These resultant plasmids were then transfected by lipofection into COS cells as previously described. Thereafter, mutants having different binding affinities to the envelope glycoprotein were screened.

(Marasco, column 31, lines 34-43). Although Marasco mentions transfecting the mutated constructs into COS cells and screening for mutants "having different binding affinities to the envelope glycoprotein," there is no indication that polynucleotides were *recovered* from the cells.

Marasco refers to a particular mutant designated "R," and sets forth the amino acid sequence of the CDR3 of this antibody; however, there is no indication that the polynucleotide encoding "R" was recovered from cells. The mutations in Marasco were made by site-directed PCR-based mutagenesis, meaning that the mutations were made *before* the clones were introduced into the COS cells. Accordingly, there would have been no reason for Marasco to have recovered the polynucleotides from the cells. Thus, contrary to the Examiner's implication, Marasco does not disclose or even suggest recovering the polynucleotide encoding "R" from cells.

Importantly, the present claims specify that the polynucleotides of the first library are recovered from host cells "which exhibit said modified phenotype." In addition to the fact that Marasco does not teach or suggest recovering polynucleotides from cells at all, Marasco certainly does not teach or suggest recovering polynucleotides from host cells that exhibit a modified phenotype. In fact, Marasco admits that "[t]hese six mutants did not bind to the HIV-1 envelope protein." (Marasco, column 31, lines 51-52). If the six mutant anti-gp120 antibodies of Marasco did not bind to the HIV-1 envelope protein, then there is absolutely no way that polynucleotides encoding these mutants could have been recovered from host cells that exhibited a modified phenotype. (It is noted that, in any event, the present claims specify that modified phenotype is induced via binding of the intracellular immunoglobulin molecule or fragment thereof to an intracellular antigen.)

(c) The Cited References Do Not Teach or Suggest Introducing a Second Library of Polynucleotides Into a Population of Eukaryotic Host Cells

Claim 1 includes "(c) introducing into said population of host cells a second library of polynucleotides encoding, through operable association with a transcriptional control region, a plurality of second intracellular immunoglobulin subunit polypeptides . . ." The Examiner has acknowledged that Marasco fails to teach the introduction of a second library of polynucleotides into a population of host cells. (Office Action, page 10). Nonetheless, the Examiner stated that "Waterhouse et al. teach screening libraries of heavy/light chain antibodies that can be 'co-selected' to produce antibodies (or fragments) with high affinity." (Office Action, page 10). Applicants respectfully disagree.

Waterhouse refers to a method of producing recombinant phage that express on their surface paired heavy and light chain variable regions. The method of Waterhouse involves the recombination of two separate vectors in *E. coli* cells. One of the vectors encodes the light chain of a first antibody ("A") and the other encodes the heavy chain of the first antibody ("B"). (*See* Waterhouse, page 2265, middle left column). According to Waterhouse:

> An *E. coli* culture harbouring vector B was infected with phage particles of vector A, and Cre recombinase provided by co-infection with phage P1Cm c1.100. Phage particles produced by growth of bacteria containing the three replicons (A, B and P1) were used to infect *E. coli* and plated on tetracycline to select cells containing [phage vector] derivatives.

(Waterhouse, page 2265, middle right column). The method of Waterhouse, therefore, requires the infection of *E. coli* cells with phage particles. Since *E. coli* are not eukaryotic cells and since phage particles can only infect bacterial cells, it follows that Waterhouse does not teach or suggest introducing libraries of polynucleotides into eukaryotic host cells, as required by the present claims. There is no indication or suggestion that the method of Waterhouse could in any way be modified to work in eukaryotic cells. Thus, the deficiencies of Marasco pointed out by the Examiner are not cured by Waterhouse.

2. A Person of Ordinary Skill in the Art Would Not Have Been Motivated to Modify or Combine the Cited References

The only portion of Marasco that even remotely relates to introducing into a population of eukaryotic host cells a library of polynucleotides that encode a plurality of intracellular immunoglobulin subunit polypeptides, each comprising an immunoglobulin variable region, is the section of Marasco which refers to screening for mutant F105 single

chain antibodies. (*See* Marasco, column 30, line 46, through column 32, line 12). This disclosure, however, falls far outside the scope of the present claims.

For one thing, the polynucleotides encoding the mutant single chain antibodies were not introduced into a eukaryotic host cell that could be induced to exhibit a predetermined modified phenotype via binding of the single chain antibodies to an intracellular antigen. Instead, the mutant polynucleotides of Marasco were introduced into COS cells. The single chain antibody of Marasco ("F105") is said to bind to an HIV-1 glycoprotein called gp120. There is no indication in Marasco that the COS cells, into which the mutant antibody-encoding polynucleotides were introduced, expressed the gp120 antigen. Even if the COS cells somehow did express the gp120 antigen, the binding of the single chain antibodies of Marasco to gp120 would not induce a "predetermined modified phenotype," as required by the present claims.

Moreover, as acknowledged by the Examiner, Marasco does not teach or suggest introducing into a population of host cells a second library of polynucleotides encoding a plurality of second intracellular immunoglobulin subunit polypeptides. The Examiner has asserted that Waterhouse cures this deficiency, but as discussed above, Waterhouse deals specifically with the introduction of polynucleotides into bacteria and relies on the use of phage particles to infect bacterial cells. Thus, the method of Waterhouse is specific for bacteria and cannot be used in the context of eukaryotic cells.

In addition, a person of ordinary skill in the art would have had absolutely no motivation to modify the screening method of Marasco by introducing a *second* library of polynucleotides into the cells, as specified by the present claims. The F105 single chain

antibody of Marasco contains *both* a heavy chain variable region *and* a light chain variable region. (*See* Marasco, Fig. 2). Thus, the F105 single chain antibody -- by itself -- is capable of binding to the gp120 antigen. Accordingly, a person of ordinary skill in the art would have had no reason to introduce even a *single* second polynucleotide encoding a second immunoglobulin subunit polypeptide into the cells used in Marasco, much less a *library* of polynucleotides encoding a plurality of intracellular immunoglobulin subunit polypeptides, as required by the present claims.

The Examiner stated that "a person of ordinary skill in the art would have been motivated to use two libraries to increase the affinity of the antibody." The Examiner has not explained how the addition of a second library encoding a plurality of second intracellular immunoglobulin subunit polypeptides could possibly "increase the affinity" of the single chain antibody of Marasco. Indeed, the addition of an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region to a single chain antibody would *not* be expected to increase the affinity of the single chain antibody for its antigen. Thus, it necessarily follows that a person of ordinary skill in the art would have had no motivation to modify or combine the cited references.

The Examiner has cited to Waterhouse as allegedly stating that the need for high efficiency antibodies "may be fulfilled by screening both heavy and light chains." (Office Action, page 11). Applicants note that Waterhouse suggests that "the creation of extremely large combinatorial repertoires" can be accomplished by "providing a light chain repertoire in [vector] A and a heavy chain repertoire in [vector] B." However, neither Waterhouse nor Marasco suggest a way by which one could adapt the system of Waterhouse so it could be

used in eukaryotic host cells. For example, the system of Waterhouse requires the production of recombinant filamentous bacteriophage particles that display variable heavy chain domains and variable light chain domains on their surface. (*See* Waterhouse, page 2265, top left column and bottom right column). Since the system of Waterhouse is technologically specific for bacterial cells, a person of ordinary skill in the art would have had no motivation to combine the system of Waterhouse with the screen set forth in Marasco.

3. Summary

For the reasons set forth above, a person of ordinary skill in the art would not have been motivated to modify or combine the cited references. In addition, not all elements of the currently pending claims are taught or suggested by the cited references. Thus, even if one were somehow motivated to combine Waterhouse and Marasco, a method that falls within the scope of the present claims would not be obtained. In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. Marasco In View of Waterhouse, Rowlands and Zauderer

Claims 1-36, 38-44, 53-57, 59-65 and 69-79 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Marasco in view of Waterhouse and further in view of Rowlands *et al.*, WO 93/01296 ("Rowlands") and Zauderer *et al.*, WO 00/28016, ("Zauderer"), as evidenced by International Committee on Taxonomy of Viruses and Wikipedia, the Free Encyclopedia. (Office Action, pages 11-12). Applicants respectfully traverse this rejection.

This rejection relies on the alleged combination of Marasco and Waterhouse to arrive at the subject matter of claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71 and 75-79. (*See* Office Action, page 12). Rowlands and Zauderer are cited as allegedly teaching the claim limitations that are absent in Marasco and Waterhouse. (*See* Office Action, pages 13-15). As explained in detail in *Section I.A*, above, the rejection of claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71 and 75-79 under § 103 based on Marasco and Waterhouse is in error because not all elements of the claims are taught or suggested by these references, and a person of ordinary skill in the art would not have been motivated to modify or combine the references. Neither Rowlands nor Zauderer cure the deficiencies of Marasco and Waterhouse, and neither reference provides a motivation to modify or combine the cited references to arrive at a method that falls within the scope of the currently presented claims. Applicants therefore respectfully request that the rejection of claims 1-36, 38-44, 53-57, 59-65 and 69-79 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

II. Obviousness-Type Double Patenting

A. The '456 Application In View of Marasco, Rowlands and Zauderer

Claims 1-36, 38-44, 53-57, 59-65 and 69-79 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 84-122 of U.S. Patent Application No. 09/987,456 ("the '456 application"), in view of Marasco, Rowlands and Zauderer. (Office Action, page 17).

Applicants respectfully request that this rejection be held in abeyance until the remaining issues outstanding in this application have been resolved.

B. The '808 Application In View of Marasco, Rowlands and Zauderer

Claims 1-36, 38-44, 53-57, 59-65 and 69-79 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-128 of U.S. Patent Application No. 10/465,808 ("the '808 application"), in view of Marasco, Rowlands and Zauderer. (Office Action, page 26).

Applicants respectfully request that this rejection be held in abeyance until the remaining issues outstanding in this application have been resolved.

In addition, Applicants note that the '808 application was filed on June 20, 2003, while the present application (10/052,942) was filed on January 23, 2002. According to the MPEP § 804.I.A.1 (pg. 800-17),:

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Thus, if the nonstatutory obviousness-type double patenting rejection over the '808 application, in view of Marasco, Rowlands and Zauderer, is the only rejection remaining in the above-captioned application (*i.e.*, the "earlier filed of the two pending applications"), the double patenting rejection should be withdrawn without the need for a terminal disclaimer.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: AUG. 23, 2006

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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